REMARKS/ARGUMENTS

Responsive to the Final Office Action dated April 19, 2007, Claims 1-20 remain pending for prosecution with Claims 1 and 11 being independent. Declarations under 37 C.F.R. 1.132 executed by inventors of the present invention, Dr. Benjamin P. Warner (hereinafter "Warner") and Dr. George J. Havrilla (hereinafter "Havrilla"), are being submitted herewith and entry of the same is respectfully requested.

I. Claim Rejections - 35 U.S.C. § 103

A. Obviousness

When determining the question of obviousness, underlying factual questions are presented which include (1) the scope and content of the prior art; (2) the level of ordinary skill in the art at the time of the invention; (3) objective evidence of nonobviousness; and (4) the differences between the prior art and the claimed subject matter. Graham v. John Deere Co., 383 U.S. 1, 17-18, 148 USPQ 459, 467 (1966). Moreover, with regard to the last prong of the *Graham* inquiry, "[t]o determine whether there was an apparent reason to combine the known elements in the way a patent claims, it will often be necessary to look to interrelated teachings of multiple patents; to the effects of demands known to the design community or present in the marketplace; and to the background knowledge possessed by a person having ordinary skill in the art. To facilitate review, this analysis should be made explicit." KSR International v. Teleflex Inc., 127 U.S. 1727 (2007).

Applicant does not contest that most of the references that have been cited and relied on by the Examiner have at least marginal pertinence to the particular problem(s) solved by the present invention in that the references disclose receptor binding assays. Stratoflex, Inc. v. Aeroquip Corp., 713 F.2d 1530, 1535, 218 USPQ 8781, 8786 (Fed. Cir. 1983).

The person of ordinary skill in the art is a hypothetical person who is presumed to know the relevant prior art. Custom Accessories, Inc. v. Jeffrey-Allan Indus., Inc., 807 F.2d 955, 962, 1 USPQ2d 1196, 1201 (Fed. Cir. 1986). The level of ordinary skill in the art may be determined by looking to the references of record. In re GPAC, Inc., 57 F.3d 1573, 35 USPQ2d 1116 (Fed. Cir. 1995). The references of record in this case reveal that a moderately high level of sophistication. Thus, Applicant submits that, as substantiated by the cited references, those with at least a bachelor's degree in biochemistry or molecular biology or the like would most likely be a person with ordinary skill in this field of endeavor.

With respect to objective evidence of nonobviousness, Applicant submits that the record supports the conclusion that there are long-felt but unsolved needs met by the present invention. The present invention is directed to the particular problem of providing a method for detecting binding events and, more particularly, to estimating binding selectivities for chemicals, analogs, and drugs being tested with receptors. In particular, the present invention is directed to a need for simpler methods for measuring binding affinities and selectivities. The above-described features represent solutions to long felt needs that could not be met by the known prior art.

Additional objective evidence of nonobviousness has been previously provided. Applicant respectfully submits that the Examiner has not given sufficient weight and consideration to this evidence. For example, the previously-submitted Zhu et al. and Predki articles clearly demonstrate that, as late as February 2004, state of the art detection methods had still not met the long-felt need to a highly sensitive label-free detection strategy for detecting chemical binding between binders and members of a receptor array. Moreover, as late as February 2004, those skilled in the art had not yet employed or even suggested a strategy of using micro-x-ray fluorescence to detect chemical binding between binders and members of a

receptor array. Furthermore, the previously-submitted article regarding the 2005 win of the R&D 100 Award as well as the February 2005 Dr. Gregory Cuny letter also provides objective evidence of nonobviousness in that Dr. Cuny specifically describes the present invention as an "elegant solution" to the unmet need for label-free drug management. Finally, the previously-submitted information with regard to the commercialization and funding of the present invention by the licensee Caldera Pharmaceuticals, Inc. is strong evidence of the nonobviousness of the present invention. Commercial success is relevant to the question of obviousness because competitors would have been economically motivated to make the invention if the invention had been obvious. Minnesota Mining & Manufacturing Co. v. Research Medical, Inc., 670 F.Supp.1037, 1057 (D. Utah 1988). Moreover, the licensing of the present invention by Caldera Pharmaceuticals also supports the finding that the claimed invention is superior to existing products and is therefore a nonobvious advance over the prior art. Tennant Co. v. Hako Minuteman, Inc., 22 USPQ2d 1161, 1177 (N.D. Ill. 1991).

Finally, prima facie obviousness requires that there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the references. This motivation-suggestion-teaching test informs the Graham analysis. "To reach a non-hindsight driven conclusion as to whether a person having ordinary skill in the art at the time of the invention would have viewed the subject matter as a whole to have been obvious in view of multiple references," there must be "some rationale, articulation, or reasoned basis to explain why the conclusion of obviousness is correct." In re Kahn, (Fed. Cir. 2006). The recent *KSR International* decision by the Supreme Court has not eliminated the motivation-suggestion-teaching test to determine whether prior art references have been properly combined. Rather, in addition to the motivation-suggestion-

teaching test, the Court discussed that combinations of known technology that are "expected" may not be patentable. Stated in the affirmative, therefore, combinations are nonobvious and patentable if unexpected. In the present application, no single prior art reference nor any combination thereof (legitimate or otherwise) meets the claimed limitations of Applicant's invention.

B. Rejection of Claims 1-20

Claims 1-20 were rejected under 35 U.S.C. § 103(a) as being unpatentable over International Publication No. WO 90/15070 to Pirrung et al. in view of U.S. Patent No. 4,436,826 to Wang. For the following reasons, Applicant respectfully requests reconsideration and withdrawal of this rejection.

The Office Action asserts that Pirrung "teaches a method and device for preparing desired sequences on a substrate at known locations wherein bound material of the substrate is exposed to irradiation . . . so as to activate material and permit binding." "The substrate has a variety of uses such as screening large numbers of peptides or receptors, wherein receptors are labeled with fluorescent markers for detection." Moreover, in "an alternative embodiment the surface may comprise of [sic] cage binding members that are capable of immobilizing receptors in predefined regions of a substrate for selective activation that allow receptors that have differential affinity for one or more ligands to react . . . A specific binding substance having a strong binding affinity for the binding member and a strong affinity for the receptor or a conjugate of the receptor may be used to act as a bridge between binding members and receptors if desired. The method uses a receptor prepared such that the receptor retains its activity toward a particular ligand."

It is admitted in the Office Action that "[s]teps (a) and step (d) of claim 11 are slightly different in that it requires 'at least one untagged' potential binder. But the claim does not prohibit binding of any potential binders. The reference of Pirrung teaches step (a), wherein a screening process for one or more receptors on a substrate that are exposed to labeled antibody binders and detected by photon detection." Moreover, "Pirrung teaches step (d) of claim 11 wherein the presence or absence of a binding event between the receptors and ligands are detected." "According to Pirrung et al., receptors used in this method could be organic compounds such as polymers (oligomer), nucleic acids, peptides, drugs, cellular membranes, cells, etc. . . .[t]he binder molecule can be selected from the group consisting of agonists and antagonists for cell membrane receptors, oligonucleotides, nucleic acids, proteins, antibodies, etc.."

The Office Action further acknowledges that Pirrung "is silent with respect to X-ray fluorescence for analysis." However, it is asserted that "Wang beneficially teaches an immunoassay method for evaluating antigen and antibody binding with X-ray fluorescence." Moreover, Wang's Figure 2 "discloses that X-ray fluorescence is the preferred detector for detection of antigen and antibody binding." Further, "[m]etal ions serving as the tagging elements (i.e., binders), can be used to detect binding, as claimed." Therefore, the Examiner concludes, it would have been obvious "to select or include X-ray fluorescence in the detection methods of Pirrung, as taught by Wang because different target antigens or antibodies can be assayed simultaneously by employing different tagged mobile units and the mobile unites [sic] with the tagging elements can be recovered for disposal or reuse."

C. Discussion

Applicant respectfully traverses the Examiner's assertions as well as the Examiner's interpretation of Pirrung and Wang and submits that both references fail to teach or suggest all of the elements of independent Claims 1 and 11.

Pirrung utterly fails to teach or suggest the claimed invention. Pirrung teaches a method for building a known polymer of a known chemical sequence at known locations on a substrate by selectively applying known monomers until a polymer of a desired length and chemical sequence is obtained. This method includes exposing a photoremovable protective to light and removing the group from a selection of linker molecules. The substrate is then washed or otherwise contacted with a first monomer that reacts with exposed functional groups on the linker molecules. A second set of selected region is then exposed to light and the photoremovable protective group on the linker molecule is removed at the second set of regions. The substrate is then contacted with a second monomer containing a photoremovable protective group for reaction with exposed functional groups. This technique allows for directing light to relatively small and precisely known location on the substrate thereby making it possible to synthesize polymers of a known chemical sequence at known locations on the substrate.

The present invention, on the other hand, is directed to a method for identifying unknown polymers and the like using a library (large number of chemically related compounds and mixtures) and screening the library to determine which members of the array, if any, have certain desirable properties. The array form also facilitates the identification of a particular material on the substrate. In other words, whereas Pirrung is concerned only with building known peptides and does not concern itself with detecting binding events, the present invention is concerned with detection and identification. The Examiner's proposed combination, therefore, uses Pirrung in a way that the reference was not intended or designed to be used. See In re Gordon, 733 F.2d 900

(Fed. Cir. 1984). In fact, the proposed modification of Pirrung's method of synthesizing peptides to result in Applicant's method of detecting a binding event in unknown polymers requires a substantial reconstruction and redesign of the elements of Pirrung and it also completely changes Pirrung's principles of operation. See In re Ratti, 270 F.2d 810 (CCPA 1959). Applicant therefore respectfully submits that the Examiner's modification of Pirrung is not only impermissible but also inoperable.

With regard to independent Claim 1, Applicant submits that Pirrung fails to teach or suggest the step (a) of exposing a plurality of receptors to at least one potential binder being detectable by X-ray fluorescence. Rather, Pirrung teaches exposing an irradiated array (receptors) to radioactive tagged binders which are only detectable by autoradiographic or ultraviolet/visible light techniques. **See Warner ¶ 8(i) and Havrilla ¶ 8(i)**. Pirrung also fails to teach or suggest the step (c) of exposing each member of the array that has been exposed to at least one potential binder to X-ray radiation to induce X-ray fluorescence signal from each member of the array now bound to at least one binder. Pirrung teaches an array of unbound photo-initiated known peptides rather than an array that has been exposed to at least one potential binder. The Office Action acknowledges this failure of Pirrung to teach or suggest the claimed invention and admits that Pirrung "is silent with respect to X-ray fluorescence for analysis." Finally, Pirrung fails to teach or suggest detecting an X-ray fluorescence signal as a result of exposure to the X-ray radiation, the X-ray fluorescence signal originating from at least any binder now bound to any member of the array thereby indicating that a binding event has occurred as recited in step (d). Again, the Office Action acknowledges these failures of Pirrung to teach or suggest the claimed invention and admits that Pirrung "is silent with respect to X-ray

fluorescence for analysis." Thus, Pirrung fails to teach or suggest at least three of the four steps of Applicant's detection method as claimed in Claim 1.

With regard to independent Claim 11, Pirrung fails to teach or suggest the step (a) of exposing a plurality of receptors to at least one untagged potential binder. The Office Action itself admits that Claim 11 is different in that it requires "at least one untagged" potential binder; however, it is asserted that Claim 11 does not prohibit binding of any potential binder. Applicant respectfully submits that the test for obviousness is not whether Claim 11 teaches or suggests Pirrung, but whether Pirrung teaches or suggests Claim 11. As stated by the Office Action itself, Pirrung teaches a screening process for one or more receptors on a substrate that are exposed to labeled (i.e., tagged) antibody binders and detected by photon detection. Therefore, there is no teaching or suggestion by Pirrung to expose a plurality of receptors to at least one untagged potential binder as recited in step (a). **See Warner ¶ 8(i) and Havrilla ¶ 8(i)**. Furthermore, Pirrung also fails to teach or suggest the step (c) of exposing each member of the array that has already been exposed to at least one untagged potential binder to X-ray radiation to induce an X-ray fluorescence signal from each member of the array now bound to at least one untagged binder. The Office Action acknowledges this failure of Pirrung to teach or suggest the claimed invention and admits that Pirrung fails to disclose untagged binders and that the reference "is silent with respect to X-ray fluorescence for analysis." Finally, Pirrung fails to teach or suggest detecting an X-ray fluorescence signal resulting from exposure to the X-ray radiation from any member of the array where a binding event has occurred thereby indicating that a binding event has occurred as recited in step (d). Again, the Office Action acknowledges these failures of Pirrung to teach or suggest the claimed invention and admits that Pirrung "is silent with respect

to X-ray fluorescence for analysis." Thus, Pirrung fails to teach or suggest at least three of the four steps of Applicant's detection method as claimed in Claim 11.

Similarly, Applicant respectfully submits that Wang also fails to teach each and every element of the claimed invention and that the Office Action itself makes no assertions that Wang teaches *any* of the steps of Applicant's claimed methods. Pirrung, as the primary reference, is relied upon for that purpose. Instead, it is merely asserted by the Office Action that "Wang beneficially teaches an immunoassay method for evaluating antigen and antibody binding with X-ray fluorescence" and that "Figure 2 of the cited reference discloses that X-ray fluorescence is the preferred detector for detection of antigen and antibody binding." The Office Action therefore concludes that it would have been obvious to select or include X-ray fluorescence in the detection methods of Pirrung, as taught by Wang, because different target antigens or antibodies can be assayed simultaneously by employing different tagged binders and that the tagging elements can be recovered for disposal or for reuse.

Applicant respectfully submits that the combination proposed by the Examiner uses Wang in a way that the reference was not intended or designed to be used. See In re Gordon, 733 F.2d 900 (Fed. Cir. 1984). Applicant's method as claimed in Claim 1 requires detection of an X-ray fluorescence signal from each member of the array bound to at least one binder and Claim 11 requires that the binder be untagged. Wang, on the other hand, does not teach or suggest the detection of X-ray fluorescence from an array. Wang also does not teach or suggestion the detection of X-ray fluorescence directly from a binder. Rather, Wang detects X-ray fluorescence from a tag. In other words, without the required tag, Wang would not be able to detect any X-ray fluorescence from the array or the binder. **See Warner ¶ 8(ii) and Havrilla ¶ 8(ii)**. This fact is further evidenced by the requirement that Wang's tag be "chemically

unassociated with said reagent and are chemically protected against reaction with said target and the biological and chemical environment of said assay." In order to be chemically unassociated, Wang encloses the tag in latex or a similar coating. Similarly, Pirrung also requires radioactive tags wherein the analysis of the sample is performed on the tag or label and not on the receptors or binders themselves. In contrast, Applicant's claimed invention measures elements that are chemically associated and that are intrinsically integral to the component being measured since it is the bound array members that are being detected by X-ray fluorescence and not a "chemically unassociated" tag or label. **See Warner ¶ 8(iii) and Havrilla ¶ 8(iii)**. The Examiner's proposed modification of Pirrung and Wang therefore requires a substantial reconstruction and redesign of the elements of both references and it also completely changes the principles of operation of both Pirrung and Wang. See In re Ratti, 270 F.2d 810 (CCPA 1959). In fact, rather than teaching or suggesting the claimed invention, Pirrung and Wang actually teach away from the present invention because both references require detection of a radioactive or fluorescent tag and could not detect the binding events claimed by Applicant. U.S. v. Adams, 383 U.S. 39 (1966).

In fact, Pirrung and Wang are nothing more than a part of the background for one of the unsolved needs in the art met by the present invention. As stated in Applicant's Background of the Invention, the attachment of a fluorescent tag to a chemical or receptor could result in a conformational change which has been known to affect the binding affinity of the chemical or receptor because the tagged surrogates are structurally different from their untagged counterparts. The present invention is therefore concerned with the evaluating the binding properties of receptors and chemicals using the untagged chemical or receptor and not with a tagged surrogate.

Accordingly, Pirrung and Wang, individually and in combination, fail to teach or suggest the combination asserted by the Examiner. Further, neither of the references teaches nor suggests all of the elements of independent Claims 1 and 11 and no resultant method for estimating the binding selectivity of a chemical could have been created from these references that would meet the limitations of Claims 1 and 11. Moreover, one of ordinary skill in the art would not have arrived at Applicant's claimed invention because Applicant's invention would not be an "expected" result of the combination of these references since all of the references, individually and in combination, fail to meet all the limitations of the subject claims. Therefore, Applicant's Claims 1 and 11 and the claims depending therefrom are nonobvious.

II. Conclusion

Applicant respectfully submits the claims are in condition for formal allowance and such is courteously solicited. If any issue regarding the allowability of any of the pending claims in the present application could be readily resolved, or if other action could be taken to further advance this application such as an Examiner's amendment, or if the Examiner should have any questions regarding the present amendment, it is respectfully requested that the Examiner please telephone Applicant's undersigned attorney in this regard. Should any fees be necessitated by this response, the Commissioner is hereby authorized to deduct such fees from Deposit Account No. 11-0160.

Respectfully submitted,

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